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(54) Solid, anhydrous, pharmaceutical compositions for vaginal use

(57) Anhydrous solid pharmaceutical composition for vaginal use, comprising at least one active ingredient in a mixture with conventional carriers and excipients, containing one or more muco-adhesive polymers dispersed in the carrier. These compositions allow for longer contact between the mucosa and the active ingredient and on-site residence, maintaining an effective therapeutic concentration for longer times.

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Description

Field of the Invention

The present invention relates to pharmaceutical compositions for vaginal use.

Background of the Invention

Bioadhesive polymers have been and still are the subject of in-depth studies. Bioadhesive polymers are generally known for their ability of being bound to biological membranes.

Numerous patents have come into being which have as their object the use of muco-adhesives in the form of tablets which contain a bioadhesive layer and a non-adhesive layer containing the medicament (U.S. Patent No. 4,292,299 to the Suzuki, et al.) or controlled release treatment compositions which, when in the presence of sufficient water to swell the bioadhesive, will adhere to skin or to a mucosal membrane (U.S. Patent No. 4, 615,697 to J.R. Robinson). Other patents have been developed for muco-adhesive compositions which will bioadhesively attach to a mucosal membrane, but can be removed by tap water if one wishes. Wang et al. (EP 93305950.3) disclosed the application of polyvinyl pyrrolidone-based muco-adhesive polymers and carboxy-functional polymers (characterized by the presence of carboxyl groups in the chains forming the polymer) dispersed in a pharmaceutically acceptable vehicle, preferably water, in an amount sufficient to form a liquid suspension, preferably a gel.

Moreover, products containing a water-insoluble bioadhesive polymer and formulated as an oil-in-water emulsion for the treatment of vaginal dryness are commercially available (REPLENS$_T$ by Warner-Lambert Co.).

Compositions containing bioadhesive polymers and therapeutic agents provide the desired contact between the mucosal membrane and the composition. The composition is left in contact with the mucosal membrane for a sufficient time for the treating agent to be released over a controlled period.

It has now been found that an anhydrous solid pharmaceutical composition employing a muco-adhesive polymer dispersed in a pharmaceutically acceptable vehicle improves residence at the application site and provides a long-lasting effect.

Pharmaceutical forms employing water-insoluble mucoadhesive agents containing water are already hydrated and immediately bond to a mucosal membrane upon application. Once applied, the composition is left in contact with the mucosal membrane for a sufficient time for the treating agent to be released over a controlled period, allowing for local or systemic activity.

On the other hand, anhydrous pharmaceutical compositions containing mucoadhesive agents are hydrated only after contact with the mucosa. When the preparation is applied to the vaginal mucosa, the pharmaceutical form simultaneously disintegrates, forming an adhesive layer on the mucosa containing the active ingredient, allowing for local or systemic activity.

Summary of the Invention

The present invention relates to anhydrous solid pharmaceutical compositions for vaginal use with at least one active ingredient employing one or more muco-adhesive polymers dispersed in a pharmaceutically acceptable vehicle. In addition, the composition may also contain pharmaceutically acceptable additives. These additives include stabilizers, preservatives, excipients, binders, coloring agents, odor controlling agents and the like.

The present invention also relates to anhydrous solid pharmaceutical compositions for vaginal use consisting of one or more muco-adhesive polymers dispersed in a pharmaceutically acceptable vehicle.

Detailed Description of the Preferred Embodiments

The composition of the present invention includes anhydrous pharmaceutical compositions with one or more active ingredients and one or more muco-adhesive polymers dispersed in a pharmaceutically acceptable vehicle.

The muco-adhesive polymers used according to this invention are known to those skilled in the art. Muco-adhesive polymers suitable for use in the bioadhesive include polycarbophil, polyacrylic acid derivatives and its salts, vinylcarboxylic acid polymers and copolymers and their salts, cellulose derivatives such as methyl, ethyl, hydroxyethyl, propyl, hydroxypropyl ethers or esters, carboxymethyl ethers and others. The bioadhesive polymers may also be used in association amongst themselves, and are generally present in the composition ranging from about 0.5% to 90% by weight of the composition.

The pharmaceutically acceptable vehicle is the bulk substance through which the bioadhesive polymer(s) and the active ingredient(s) are distributed to form a dispersion. This vehicle must also be capable of being used in or on humans or other mammals without causing any ill effects, such as toxicity or severe irritation to the mucosal tissue. Pharmaceutically acceptable vehicles suitable for use in the present invention include powders, solid and semi-solid

lipid masses, and anhydrous liquids, normally used in pharmaceutical and cosmetic preparations.

The active ingredients suitable for use in the present inventi n are of different types (natural, semi-synthetic and synthetic) and include antimycotic agents, antipr tozoal agents, disinfectants, h rmones, antibiotics, chemotherapeutic agents and others) and are generally present in the composition ranging from about 0.002% to 90% by weight of the composition.

Examples of active ingredients used in the present invention are imidazole antimycotics such as miconazole, econazole, ketonazole, local antiseptics, hormones and other well known products.

The composition of the present invention may take the form of vaginal tablets, soft gelatin capsules, semi-synthetic glyceride-based suppositories, which may or may not contain surfactant substances and polyethylene glycol-based suppositories.

The dosage forms of the invention may be prepared by experts of the art according to well known techniques (see Remington's Pharmaceutical Sciences Handbook, XVII ed., Mack Pub., N.Y., U.S.A.).

A study was carried out on a total of 20 healthy female volunteers in order to compare the release rates of econazole nitrate from a conventional drug without a bioadhesive and from three formulations, each containing a different concentration of polycarbophil as mucoadhesive agent (25, 50, and 100 mg/suppository). Vaginal fluid samples were taken at 0 and at 2, 6, 12 and 24 h from administration and drug concentrations measured by HPLC. Results showed slower release rates of econazole nitrate plus the muco-adhesive as compared to the commercially available drug. High vaginal fluid drug concentrations were measured up to 24 h following the administration of the vaginal suppositories containing polycarbophil while no drug was detected 12 h following the administration of the commercially available product.

Table

Econazole levels (mg/ml) in vaginal fluid					
Product					
Time (hours)	**0**	**2**	**6**	**12**	**24**
Commercial product	0	48.6	0.85	0	0
Formulation 1	0	56.4	44.7	36.9	0.12
Formulation 2	0	88.7	54.3	28.9	12.6
Formulation 3	0	96.8	68.3	46.3	18.9

The sustained release of the drug is regulated by the presence of the muco-adhesive polymer.

The use of one or more muco-adhesive polymers in the manufacture of anhydrous solid vaginal pharmaceutical compositions with controlled release fall within the scope of the present invention.

The present invention also relates to anhydrous solid pharmaceutical compositions for vaginal use consisting of one or more muco-adhesive polymers dispersed in a pharmaceutically acceptable vehicle.

The following examples further illustrate the invention.

Example N. 1: Vaginal suppositories containing an antimycotic Econazole Nitrate (active ingredient)	
Component	Unitary Formula
Econazole Nitrate	100 mg
Policarbophyl (Noveon$^{(R)}$ AA1)	100 mg
Semi-synthetic Triglicerides (m.p. 37°C)	q.s. to 3 g

Example N. 2: Vaginal tablets containing Metronidaz le (active ingredient)	
Component	Unitary Formula
Metronidazole	500 mg
Hydroxypropylmethyl-cellulose (Methocel(R) K4M)	100 mg
Microcrystalline Cellulose (Avicel PH102)	290 mg
Granular Lactose	200 mg
Talc	5 mg
Magnesium Stearate	5 mg

Example N. 3: Soft-gelatine capsules containing Clindamycin (active ingredient)	
Component	Unitary Formula
Clindamycin base	100 mg
Carboxyvinylpolymer (Carbopol(R) 974P)	50 mg
Labrafil(R)	q.s. to 500 mg
Gelatin shell	q.s.

Example N. 4: Vaginal suppositories containing an antimycotic Miconazole Nitrate (active ingredient)	
Component	Unitary Formula
Miconazole Nitrate	100 mg
Policarbophyl (Noveon(R) AA1)	200 mg
Polyethylene-glycol mixture	q.s. to 3 g

Example N. 5: Vaginal suppositories containing Povidone-Iodine (active ingredient)	
Component	Unitary Formula
Povidone-Iodine (Iodine 10%)	200 mg
Policarbophyl (Noveon(R) AA1)	200 mg
Polyethylene-glycol mixture	q.s. to 3 g

Example N. 6: Soft-gelatine capsules containing Estriol (active ingredient)	
Component	Unitary Formula
Estriol	0.5 mg
Policarbophyl (Noveon(R) AA1)	50 mg
Labrafil(R)	q.s. to 500 mg
Gelatin shell	q.s.

Claims

1. Anhydrous solid pharmaceutical compositions for vaginal use with at least one active ingredient employing one or more muco-adhesive polymers dispersed in a pharmaceutically acceptable vehicle.

2. Compositions according to claim 1, wherein the mucoadhesive agents are present in the composition ranging from 0.5% to 90% by weight of the composition.

3. Compositions according to claims 1 and 2, wherein the muco-adhesive polymer(s) are selected from the group consisting of polycarbophil, polyacrylic acid derivatives and its salts, vinylcarboxylic acid polymers and copolymers and their salts, cellulose derivatives such as methyl, ethyl, hydroxyethyl, propyl, hydroxypropyl ethers or esters, carboxymethyl ethers.

4. Compositions according to claims 1 through 3 wherein the active ingredient(s) are selected from the group consisting of antimycotic agents, antiprotozoal agents, disinfectants, hormones, antibiotics, chemotherapeutic agents.

5. Compositions according to claims 1 through 4 in the form of vaginal tablets, soft gelatin capsules, semi-synthetic glyceride-based suppositories, which may or may not contain surfactant substances and polyethylene glycol-based suppositories.

6. Use of mucoadhesive polymers in the development and manufacture of controlled-release, anhydrous, solid pharmaceutical compositions.

7. Anhydrous solid pharmaceutical compositions for vaginal use consisting of one or more muco-adhesive polymers dispersed or dissolved in a pharmaceutically acceptable vehicle.

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EUROPEAN SEARCH REPORT

Application Number
EP 96 11 6870

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	FR-A-2 335 203 (MARCY JEAN) 15 July 1977 * page 1, line 36-38 * * page 2, line 39 - page 3, line 5 * * page 4, line 4-7 * * page 4, line 14-20 *	1-7	A61K9/10 A61K9/02 A61K9/48
X	US-A-4 853 211 (KUROBE TOSHIO ET AL) 1 August 1989 * column 5; example 3 *	1-7	
D,X	US-A-4 292 299 (SUZUKI YOSHIKI ET AL) 29 September 1981 * column 2, line 43-64 * * column 10, line 60-68 *	1-3,6,7	
X	EP-A-0 153 836 (HEALTH PRODUCTS DEV INC) 4 September 1985 * page 10; example 8 *	1,2,5-7	
A	US-A-5 369 131 (POLI STEFANO ET AL) 29 November 1994 * column 2, line 20-26 *	1-7	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	13 January 1997	Herrera, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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& : member of the same patent family, corresponding document

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